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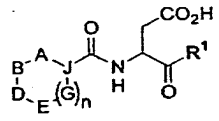
(54) Title: SMALL MOLECULE INHIBITORS OF CASPASES



(I)

(57) Abstract: The present invention provides compounds having formula (I); and pharmaceutically acceptable derivatives thereof, wherein A, B, D, E, G, J, n, and R^1 are as described generally and in classes and subclasses herein, and additionally provides pharmaceutical compositions thereof, and methods for the use thereof as caspase inhibitors and for the treatment of disorders caused by excessive apoptotic activity.

SMALL MOLECULE INHIBITORS OF CASPASES

PRIORITY CLAIM

[0001] The present application claims priority under 35 U.S.C. § 119 to U.S.S.N. 60/323,270, filed September 18, 2001, and U.S.S.N. 60/371,762, filed April 11, 2002, the entire contents of each of these applications are incorporated herein by reference.

BACKGROUND OF THE INVENTION

[0002] Apoptotic cell death is a fundamentally important biological process that is required to maintain the integrity and homeostasis of multicellular organisms. Inappropriate and excessive apoptosis, however, underlies the etiology of many of the most intractable of human diseases. The apoptotic pathway is predominantly executed by a series of cysteine proteases designated the "caspases" (cysteinyl aspartate-specific proteinases). Caspases are intracellular protease enzymes that play significant roles in both cytokine maturation and programmed cell death (apoptosis) (see, Thornberry *et al., Nature* **1992**, *356*, 768-774; Thornberry *et al. Chem. Biol.* **1998**, *5*, R97-103). Specifically, caspases are responsible for the proteolytic degradation of more than 100 different protein substrates, including proteins involved in DNA repair, nuclear membrane integrity, and cell structural integrity.

[0003] The first caspase to be discovered was Interleukin-1β Converting Enzyme (ICE), now also known as caspase-1 (Thornberry *et al.* 1992, *Nature* **356**:768-774; Cerretti *et al.* 1992, *Science* **256**:97-99). Caspase-1 was initially identified as the protease that cleaves the immature pro-IL-1β polypeptide to produce the mature IL-1β polypeptide, a critical step that precedes secretion of IL-1β from the cell. Since IL-1β is an important mediator of inflammation, it has been suggested that disruption of caspase-1 activity may reduce the inflammatory response after exposure to an appropriate stimulant. This was shown to be the case in mice containing a "knockout" of the caspase-1 gene. These mice undergo normal development but are deficient in mounting a normal inflammatory response (Kuida *et al.* 1995, *Science* **267**:2000-2003; Li *et al.* 1995, *Cell* **80**:401-411). Even though the predominant role of caspase-1 appears to involve the inflammatory pathway, evidence indicates that it is also important for the apoptotic pathway, since these mice also show reduced levels of apoptosis when treated with chemicals that typically induce apoptosis.

[0004] To date, approximately eleven caspases have been identified in humans. Caspases have been broadly categorized into three main functional categories. Group I caspases (*e.g.* caspase-1, -4 and –5) are predominantly involved in the inflammatory response pathway,